UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,658	06/22/2006	Michael Gotthardt	BB-156	4607

23557 7590 10/01/2007

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,658	GOTTHARDT ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-34* is/are pending in the application.

4a) Of the above claim(s) *1-9,11,12 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-26 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on August 2, 2007 is acknowledged.

Applicant has elected the invention of Group II, claims 13-26 and 31-34, drawn to a method for producing an inducible site-directed transgenic cell or organism comprising a mutated allele of a gene and a rescue allele of said mutated gene.

Within Group II, Applicant has elected the following species:

i) wherein the alternative structural elements to the genetic construct encoding the rescue allele, is a recombination target site, as recited in claim 15, specifically a Lox site;

ii) wherein the alternative mechanisms by which the rescue allele inhibits the function of a non-mutated allele, as recited in claim 16, is direct inhibition;

iii) wherein the specific number of mutated alleles, as recited in claim 20, is one;

iv) wherein the specific number of rescue alleles, as recited in claim 20, is one;

v) wherein the alternative host cell types, as recited in claim 19, is a mammalian cell;

vi) wherein the alternative biological subjects, as recited in claim 25, is a mammalian tissue;

vii) wherein the alternative inactivation techniques, as recited in claims 23 and 33, is via site-directed recombination via Cre/Lox;

viii) wherein the alternative settings in which the method is practiced, as recited in claim 24, in vivo;

ix) wherein the alternative temporal and/or local phenotypes, as recited in claim 32, is an embryonic lethal phenotype; and

x) wherein the alternative mutagenesis techniques, as recited in claim 31, is random integration of foreign DNA.

2. Election of Applicant's invention(s) was made without traverse.

Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without

traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

3. Claims 1-9, 11-12 and 27-30 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 13-26 and 31-34 are under consideration.

Priority

5. This application is a 371 of PCT/EP04/02216, filed March 4, 2004. Applicant's claim for the benefit of the prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is made of Applicant's claim for foreign priority of EPO 03008470.1, filed April 11, 2003 under 35 U.S.C. 119(a)-(d). A certified copy has been filed in the instant application.

Accordingly, the effective priority date of the instant application is granted as April 11, 2003.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on January 3, 2006 that have been considered. Citation R1 (Bockamp et al) is corrected to read "December 3, 2002" because it was available online December 3, 2002 and the publication is stamped with a 2002 date, not a 2003 date (see pg 115, upper right corner). The signed and initialed PTO Forms 1449 are mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

6. **Claims 13-18, 22-23 and 26 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 13 and 26 are indefinite in the recitation of the term "optionally". It is unclear whether any of the limitations which follow the term "optionally" are required limitations, i.e. are the further steps of cultivating the target cell under conditions that allow for a selection of cells that contain both the mutated allele and the rescue allele of said gene are "optional", or critical? Therefore the metes and bounds of this claim are unclear.

Claims 13-14, 22-23 and 26 and 31 are indefinite in the recitation of the term "suitable". The term "suitable" in claims 13 and 26 is a relative term which renders the claim indefinite. The term "suitable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "suitable" is a subjective term because suitability is not specifically defined in the art and is subject to change from one artisan to the next. The metes and bounds are relative to the artisan's interpretation and not specifically defined in the art.

Claims 13 and 26 recite in part (b) "a rescue allele of said gene that can be conditionally inactivated". It is not clear if the rescue allele is subject to conditional inactivation or if the "gene to be mutated" recited in part (a) is to be "conditionally inactivated", that is to say, the mutated allele is a conditionally-regulated.

Claims 13 and 26 (and dependent claims) are vague in that no step(s) in the claimed method refers back to or recapitulates the preamble of the claim. Applicants recite a method of producing an inducible site-directed mutant cell capable of conditional gene rescue, but no step is recited that actually accomplishes the preamble. It is unclear if additional, undisclosed steps are a part of the claimed method and therefore the metes and bounds of the claimed subject matter are unclear.

Claim 15 recites a genetic construct comprising recombination sites, e.g. Lox sites. However, the purpose or function of the recombination sites relevant to the claimed method is not claimed.

Claim 16 recites the rescue allele should have the property of directly inhibiting the function of any non-mutated copy of a mutated allele. As a first matter, the juxtaposition of "non-mutated copy of a mutated allele" indicates that the "mutated allele" is no longer mutated. It is unclear by what method steps the mutated allele is to become non-mutated. As a second matter, it is unclear which activity is being inhibited by the rescue allele—that encoded by the "mutated allele" or that encoded by the wildtype allele? If the rescue allele inhibits the activity of the wildtype allele, then the term "rescue" as per the instant invention is not clearly defined because one of ordinary skill in the art would understand the term "rescue" to be essentially equivalent to "wildtype", wherein the rescue allele would not inhibit the activity of the wildtype allele.

Claim 17 recites "tissue specific". It is unclear if the mutated allele is also tissue specific.

Claim 18 recites the limitation "said allele" in reference to Claim 13. There is insufficient antecedent basis for this limitation in the claim. Claim 13 recites a plurality of alleles, and thus it is not clear which allele is to encode *titin*.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. **Claims 13-14, 16, 20-22, 24 and 26 are rejected under 35 U.S.C. 102(b)** as being anticipated by Roemer et al (WO 01/60975; *of record in IDS).

With respect to claims 13 and 26, Roemer et al disclose a method for creating a diploid mutant cell of an organism in which the dosage of a specific gene can be modulated. By this

method of the invention, one allele of a target gene in a diploid cell of an organism is disrupted [a mutated allele] while the second allele is modified by having its promoter replaced by a regulated promoter of heterologous origin [a conditionally inactivated rescue allele] (pg 10, lines 1-5), referred to herein as the GRACE method, where the acronym is derived from the phrase Gene Replacement And Conditional Expression.

With respect to claim 14, Roemer et al disclose the mutagenesis technique may comprise gene inactivation by insertion or replacement of a nucleotide sequence (pg 5, lines 1-2), wherein the process may be repeated with each and every gene of the organism (substitution).

With respect to claim 16, the Examiner interprets the claim to mean that the conditionally inducible rescue construct is able to supplant the function caused by the mutated allele. In the instant case, Roemer et al teach the conditionally inducible rescue construct is able to restore those functions/activities rendered mutant by the mutated alleles (pg 7, lines 1-11).

With respect to claim 20, Roemer et al disclose the use of diploid organisms, wherein a first allele is rendered mutant and a second allele is rendered conditionally-inactivatable rescue allele.

With respect to claim 21, Roemer et al disclose the method useful for identifying genes required for growth, viability and survival (pg 5, lines 4-6; pg 83, lines 34-35).

With respect to claim 22, Roemer et al disclose the suitable inactivation technique via a tetracycline-regulatable promoter (pg 18, 5.2.2).

With respect to claim 24, Roemer et al disclose the method to be performed in vivo, as applied to yeast cells (pg 16, 5.2).

8. **Claims 13-17, 19-22, 24-26 and 34 rejected under 35 U.S.C. 102(b)** as being anticipated by Shin et al (Nature 402:496-501, 1999).

With respect to claims 13, 19, 24-26 and 34, Shin et al teach a method for generating a transgenic mouse comprising a mutated allele of the *Endrb* gene that has been "knocked-in" to replace the endogenous wildtype *Endrb* alleles, generating $Endrb^{-/-}$, said $Endrb^{-/-}$ mice further comprising a rescue allele under the control of a tetracycline-inducible promoter "knocked-in" to

the second endogenous wildtype *Endrb* allele, thereby rendering the rescue allele capable of conditional inactivation (pg 497, Figure 1).

With respect to claim 14, Shin et al teach the replacement of the *Endrb* first exon and 230 base pairs of the first intron with tTA or rtTA coding region linked of the rabbit β-globin intron/polyadenylation sequences (pg 496, col. 2, Incorporation).

With respect to claim 15, Shin et al teach the rescue allele genetic construct comprises Lox P sites (pg 497, Figure 1).

With respect to claim 16, the Examiner interprets the claim to mean that the conditionally inducible rescue construct is able to supplant the function caused by the mutated allele. In the instant case, Shin et al teach the conditionally inducible rescue construct is able to restore those ENDRB functions/activities rendered absent by the *Endrb* mutated alleles (entire paper).

With respect to claim 17, because the tTA or rtTA is under the control of the endogenous Endrb transcriptional regulatory elements, both the mutated allele and the rescue allele are considered to be inherently tissue-specific to the same extent as endogenous *Endrb* expression is tissue-specific, absent evidence to the contrary.

With respect to claim 20, Shin et al teach the double knock-in transgenic mice to comprise one mutated allele and one rescue allele (pg 497, Figure 1).

With respect to claim 21, Shin et al teach the Endrb mutant mice have temporal and/or local phenotypes due to defective melanocyte migration and megacolon leading to death (pgs 498-499).

With respect to claim 22, Shin et al teach the suitable inactivation technique to be the presence or absence of doxycycline (pg 497, Figure 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. **Claims 13-22, 24-26, 32 and 34 are rejected under 35 U.S.C. 103(a)** as being obvious over Shin et al (Nature 402:496-501, 1999) and Gotthardt et al (J. Biol. Chem. 278(8): 6059-6065, 2003; available online December 2, 2002; *of record in IDS).

Shin et al teach a method for generating a transgenic mouse comprising a mutated allele of the *Endrb* gene that has been "knocked-in" to replace the endogenous wildtype *Endrb* alleles (*Endrb*$^{-/-}$), said *Endrb*$^{-/-}$ mice further comprising a rescue allele under the control of a tetracycline-inducible promoter "knocked-in" to the second endogenous wildtype *Endrb* allele, thereby rendering the rescue allele capable of conditional inactivation (pg 497, Figure 1). The double knock-in transgenic mice to comprise one mutated allele and one rescue allele (pg 497, Figure 1). The mutated allele comprises the replacement of the *Endrb* first exon and 230 base pairs of the first intron with tTA or rtTA coding region linked of the rabbit β-globin intron/polyadenylation sequences (pg 496, col. 2, Incorporation). Shin et al teach the Endrb mutant mice have temporal and/or local phenotypes due to defective melanocyte migration and megacolon leading to death (pgs 498-499). The rescue allele genetic construct comprises Lox P sites (pg 497, Figure 1) and is conditionally inactivated via the presence or absence of doxycycline (pg 497, Figure 1). Because the tTA or rtTA is under the control of the endogenous Endrb transcriptional regulatory elements, both the mutated allele and the rescue allele are considered to be inherently tissue-specific to the same extent as endogenous *Endrb* expression is tissue-specific, absent evidence to the contrary. To the extent that the Examiner interprets claim

16 to mean that the conditionally inducible rescue construct is able to supplant the function caused by the mutated allele, Shin et al teach the conditionally inducible rescue construct is able to restore those ENDRB functions/activities rendered absent by the *Endrb* mutated alleles (entire paper).

Shin et al do not teach wherein the mutated and rescue alleles encode *titin*, or wherein the mutated allele causes an embryonic lethal phenotype. However, at the time of the invention, Gotthardt et al taught a method of making *titin* kinase domain-deficient mice that died as early embryos.

It would have been obvious to one of ordinary skill in the art to substitute the *Endrb* target gene of Shin et al with the *titin* target gene as taught by Gotthardt et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Shin et al taught how to combine a mutated allele and a regulated rescue allele at a single locus. Gotthardt et al taught that the *titin* locus is amenable to gene-targeted homologous recombination to create mutated alleles resulting in embryonic lethal effects. The ordinary artisan would need merely to transfer the technology taught by Shin et al and apply it to make the analogous genetic constructs towards the *titin* locus of Gotthardt et al, wherein the mutated allele would be reasonably expected to yield the embryonic lethal phenotype in the absence of the conditional activation of the rescue allele.

Thus, the invention as a whole is *prima facie* obvious.

10. **Claims 13-17, 19-25 and 34 are rejected under 35 U.S.C. 103(a)** as being obvious over Roh et al (Mol. Endocrinol. 15(4): 600-613, 2001) and Tian et al (Developmental Biology 242:204-223, 2002).

Roh et al teach a method of making a transgenic mouse encoding a mutated allele of a gene, wherein said mutated allele comprises a mutation at the exon or sub-exon level, e.g. a deletion, such that the mutant allele encodes a truncated EGF receptor (pg 601, col. 1, ¶2), wherein the genetic construct comprising the mutated allele has integrated randomly into the host genomic DNA. The mutated allele is under the control of tetracycline-controlled transactivator (tTA), wherein expression of tTA is under the control of an exogenous promoter (pg 601, col. 1,

¶1), therefore the mutated allele is considered to be tissue-specific as per the tissue-specificity of the exogenous promoter regulating expression of tTA. The bi-transgenic mice (PRL-tTA/TetRE-EGFRtr) displayed adverse temporal and local phenotypes such as delayed eye opening and obvious dwarf phenotypes (pg 606, col. 2; pg 608, Figure 6).

Roh et al do not teach the transgenic mouse to further comprise a conditionally-inactivatable rescue allele, wherein the conditional inactivation is mediated by Cre/Lox site-specific recombination.

However, at the time of the invention, Tian et al taught a method of making a conditional rescue allele in mice, wherein the rescue allele is inactivated via Cre-mediated recombination that acts on Lox recognition target sites (Cre/Lox) to catalyze recombination between to (Lox) recognition sites to bring about modification of the associated DNA, specifically a deletion (pg 205, Figure 1). Because the Cre-mediated recombination event is under the control of an exogenous promoter-Cre transgene, e.g. a CAG-promoter (pg 208, col. 2), the rescue allele is considered to be subject to tissue-specific conditional regulation. To the extent that the Examiner interprets claim 16 to mean that the conditionally inducible rescue construct is able to supplant the function caused by the mutated allele, Tian et al teach the conditionally inducible rescue construct is able to encode a wildtype open reading frame (pg 207, Figure 2).

It would have been obvious to one of ordinary skill in the art to combine the regulated mutated allele technology as taught by Roh et al with the regulated rescue allele technology as taught by Tian et al with a reasonable chance of success because all the claimed elements [regulated mutated allele technology and regulated rescue allele technology] were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The artisan need only cross a transgenic non-human organism, e.g. mouse, comprising a regulated mutated allele of the artisan's desired target gene to a transgenic non-human organism, e.g. mouse, comprising a regulated rescue allele of the artisan's desired target gene so as to combine both transgenes into the same transgenic non-human organism, wherein expression of the mutated allele and the rescue allele may each be regulated by known means coincidentally or sequentially, as per the needs of the artisan.

Thus, the invention as a whole is *prima facie* obvious.

11. **Claims 13, 18, 26 and 32 are rejected under 35 U.S.C. 103(a)** as being obvious over Roh et a (Mol. Endocrinol. 15(4): 600-613, 2001) and Tian et al (Developmental Biology 242:204-223, 2002), as applied to claims 13-17, 19-25 and 34 above, and in further view of Gotthardt et al (J. Biol. Chem. 278(8): 6059-6065, 2003; available online December 2, 2002; *of record in IDS).

Roh et al and Tian et al do not teach wherein the mutated and rescue alleles encode *titin*, or wherein the mutated allele causes an embryonic lethal phenotype. However, at the time of the invention, Gotthardt et al taught a method of making *titin* kinase domain-deficient mice that died as early embryos.

It would have been obvious to one of ordinary skill in the art to substitute the mutant and rescue alleles of Roh et al and Tian et al with the *titin* target gene as taught by Gotthardt et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Roh et al and Tian et al taught how to make a mutated allele and a conditional rescue allele. Gotthardt et al taught that the *titin* locus is amenable to gene-targeted homologous recombination to create mutated alleles resulting in embryonic lethal effects. The ordinary artisan would need merely to transfer the technology taught by Roh et al and Tian et al and apply it to make the analogous mutated allele and rescue allele genetic constructs as applied to the *titin* locus of Gotthardt et al, wherein the mutated allele would be reasonably expected to yield the embryonic lethal phenotype in the absence of the conditional activation of the rescue allele.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036.

The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Q. JANICE LI, M.D.
PRIMARY EXAMINER